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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/606,879	06/27/2003	Lieven Stuyver	BJS-2551-123	5237

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EXAMINER	
PENG, BO	
ART UNIT	PAPER NUMBER
1648	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/606,879	STUYVER ET AL.	
	Examiner	Art Unit	
	BO PENG	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-32 and 34* is/are pending in the application.

4a) Of the above claim(s) *18-27,30-32 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17, 28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 12, 2008, has been entered.

2. Claims 15-32 and 34 are pending. Claims 18-27, 30-32 and 34 are nonelected. Claims 15-17, 28 and 29 are examined in the instant Office action.

Foreign Priority

3. Acknowledgment is made of applicant's claim for priority based on PCT/EP97/02002 filed April 21, 1997 and foreign priority based on EP 96870053 filed on April 19, 1996. Receipt is acknowledged of the paper of PCT/EP97/02002 filed on April 21, 1997, which has been placed of record in the file. It is noted, however, that the paper and the certified copy of EP 96870053 filed on April 19, 1996, have not been received. The examiner could not locate the file of EP 96870053 from EPO website, either.

4. A review of the priority document of PCT/EP97/02002 shows support for primers SEQ ID NOs: 75, 76, 94, 105, 112, 134 and 135. It is not clear, however, whether the foreign priority document EP 96870053 provides written description for the claimed primers. Therefore, for purposes of examination, the priority date for Claims 15-23 has been currently determined to be April 21, 1997, the filing date of PCT/EP97/02002.

5. Applicant is reminded that in order for a patent issuing on the instant application to obtain the benefit of priority of EP 96870053 filed on April 19, 1996, under 35 U.S.C. 119(a)-(d) or (f), a claim for such foreign priority must be timely made with the paper of EP 96870053.

Claim Rejections - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. (**New rejection**) Claims 15 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

8. In making a determination as to whether a claimed invention has been adequately described, the courts have identified certain elements that may be considered. Among those elements are the knowledge in the particular field, the extent and content of the prior art, the maturity of the technology, and predictability of the aspect at issue. See e.g., *Capon v. Eshhar*, 76 U.S.P.Q. 2d 1078, at 1085 (CAFC 2005). For a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical **genus**, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In

> other cases, particularly but not necessarily, chemical cases, **where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...**")
> *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

9. Claims 15 and 29 read on a method for determining the presence or absence of HBV genotype A in a biological sample, comprising hybridizing a nucleic acids isolated from the sample with a nucleotide probe of about 5 to 50 nucleotides long, hybridizing specifically a HBV genotype A specific target sequence in the HBsAg region of HBV.

10. The scope of the claims encompasses use of any undefined nucleotide probes of about 5 to 50 nucleotides long to specifically detect a sub-genus of HBV genotype A, but not other HBV genotypes in a sample. In supporting these claims, the instant specification has disclosed a few species of genotype A- specific probes, such as SEQ ID NO: 77, which can specifically hybrid the target sequences SEQ ID NOs: 297 to 313 of HBV genotype A shown in Figure 1. However, the specification has not identified the other genotype A-specific target sequences of HBV.

11. The court indicates: "The presence of multiple species within a claimed genus does not necessarily demonstrate possession of the genus. See, In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973) (stating "where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed at a later date in the prosecution of a patent application."); and University of California v. Eli Lilly and Co., 43 USPQ2d 1398, at 1405 (Fed Cir 1997)(citing Smyth for support).

12. The art indicates several forms of uncertainty regarding the ability of undefined nucleotide probes of about 5 to 50 nucleotides long to specifically detect a sub-genus of HBV genotype A by hybridization. First, the art indicates that it is not certain which are genotype A-

specific target sequences of all HBV viruses encompassed in the scope of the claims. The art teaches that genomes of HBV viruses have a high degree of variation. HBV genotypes are characterized by an inter-group divergence in nucleotide sequence of 8% or greater (Okamoto, 1988, see abstract). The prior art also indicates that an HBV genome is continually subject to variation, and has an estimated nucleotide substitution rate per site per year of 1.4×10^{-5} to 3.2×10^{-5} (Okamoto, J. Gen. Virol. 1988, 69:2575-2583, cited in IDS; see e.g. Para 3, p.2579). In the persistently infected patients, the daily HBV turnover is approximately 50% of free virus population, with a total release of 10^{11} virus particles per day in the peripheral blood (Stuyver, Hepatology, 2001; 33:751-757, see e.g. right col. p. 752). Moreover, the art indicates that in clinical settings, the genotype of HBV viruses is usually unknown (Stuyver 2001, Para 2, left col. p. 752). The relevance of wild-type HBV to known HBV is mostly speculative. Given the high variability of HBV viruses, and the unknown sequences of all HBVs, one of ordinary skill in the art cannot envision which are genotype A-specific target sequences of all HBV viruses encompassed in the scope of the claims without an adequate description in the specification.

13. However, the instant specification has failed to provide an adequate description of genotype-A-specific target sequences to address the uncertainties regarding HBVs sequence identities in the art. Although the specification teaches a few strains of HBV genotype A and sequence comparison with a few strains of other genotypes of HBV, a few known HBV strains are not representative numbers of all genotype HBVs because of the high variability within HBV.

14. Secondly, Claims 15 and 29 describe use of undefined nucleotide probes of about 5 to 50 nucleotides long to specifically detect a sub-genus of HBV genotype A, not other genotypes,

under any hybridization conditions. The application provides no demonstrations regarding the effect of undefined nucleotide probes of about 5 to 50 nucleotides long to specifically hybrid a sub-genus of HBV genotype A, not other genotypes, under any hybridization conditions.
It is known in the art that the design of genotype-specific probes needs knowledge of genotype-specific sequences. However, because of a lack of description of genotype A-specific target sequences of all HBVs, one of ordinary skill in the art would not know what are nucleotide probes of about 5 to 50 nucleotides long that specifically detect a sub-genus of HBV genotype A, not other genotypes. Although the specification has disclosed a few species of genotype A-specific probes, such as SEQ ID NO: 77, one of ordinary skill in the art has no basis on which to predict the other genotype A-specific target sequences encompassed in Claim 15 because the high variability of HBV. Therefore, the few species of genotype-A specific probes disclosed in the specification are not sufficiently representative of genotype-A-specific probes of about 5 to 50 nucleotides long that can specifically hybridize HBV genotype A. For the reasons discussed above, the specification has not provided an adequate description that allows one of skill in the art to predict other genotype A-specific probes, or distinguish members of the claimed sub-subgenus of genotype A-specific probes from non-genotype A probes.

15. Given the high degree of variability that exists in HBV viruses, and the number of species required to form a representative number varies proportionally with the degree of variability within the claimed genus, while the skilled artisan could reasonably conclude Applicant was in possession of a method of detecting genotype A by using a specific probe, such as SEQ ID NO: 77, to hybrid sequence related HBV target sequences, those of ordinary skill in the art would not consider the applicant to have been in possession of the entire breath of the claimed genus of

genotype A-specific probes based on a few species disclosed, and the alleged method.

Claim Rejections - 35 USC § 112

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. (**New rejection**) Claims 15, 16, 17, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting genotype A HBV by hybridizing HBV using indicated genotype-A-specific probe, e.g. SEQ ID NO: 77, under a stringy hybridization condition, does not reasonably provide enablement for the method of detecting genotype A HBV using undefined probes under any hybridization conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

18. As discussed above, since the Claims 15 and 29 lack adequate description of genotype A specific target sequences, and genotype A specific nucleotide probes, one of ordinary skill in the art would not know how to make genotype A specific probes, thereby would not know how to use the alleged invention commensurate in scope with these claims.

19. Furthermore, it is known within the art that a probe can hybrid a DNA/or RNA that share the same sequence as the probe under high stringy hybridization condition. However, the same probe can also hybridize (mismatch) other un-related sequences of other genotype HBV under low stringy hybridization condition. Here, the claims allege use of undefined nucleotide probes of about 5 to 50 nucleotides long to specifically detect a sub-genus of HBV genotype A, not

other genotypes, under any hybridization conditions. The instant specification has not demonstrated how any nucleotide probes of about 5 to 50 nucleotides long can specifically hybrid to genotype A-specific target sequences under any hybridization condition, especially low stringy condition. Thus, in view of the limited teachings of the present application, the teachings in the art indicating uncertainty in the operation of the claimed method, the alleged method does not enable for determining "the presence or absence of HBV genotype A in a biological sample". One of ordinary skill in the art cannot use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. **(Prior rejection-withdrawn)** The rejection of Claims 15 and 16 under 35 U.S.C. 102(b) as being anticipated by McDonough (EP0569237A2, 1993) **is withdrawn** in view of Applicant's argument.

35 USC § 103

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as

> set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. **(Prior rejection-withdrawn)** The rejection of Claims 15-17, 28 and 29 under 35 U.S.C. 103(a) as being obvious over McDonough, Maertens (WO 94/12670) and Ashton-Rickard (1989), **is withdrawn** in view of Applicant's argument.

24. **(New rejection)** Claims 15, 16, and 29 are rejected under 35 U.S.C. 103(a) as being obvious over, Maertens (WO 94/12670), in view of Okamoto (J. Gen Virol. 69,2575-2583, 1988) and Norder (J. Gen Virology 73, 1201-12-8, 1992).

25. Claims 15, 16 and 29 are directed to a method for determining the presence or absence of HBV genotype A in a biological sample, comprising: (i) optionally releasing, isolating and/or concentrating the polynucleic acids present in the sample; (ii) optionally amplifying the HBsAg region, or part thereof, of the HBV gene present in said sample with at least one suitable primer pair; (iii) hybridizing the polynucleic acids of step (i) or (ii) with at least one nucleotide probe of about 5 to 50 nucleotides long hybridizing specifically to a HBV genotype A specific target sequence in the HBsAg region of HBV; (iv) detecting the hybrid(s) formed in step (iii); (v) inferring the HBV genotype present in said sample from the hybridization signal(s) obtained in step (iv), wherein the HBV genotype A specific target is selected from the group consisting of SEQ ID NOs: 279-313, wherein step (iii) is a reverse hybridization step.

26. Maertens teaches a line probe assay (LiPA) for genotyping viruses, such as HCV, HIV, HBV and/**or** HTLV present in biological samples (see p. 25). Maertens teaches the method comprises the steps of providing at lease one of the probes of HCV and at least of one of the

probes capable of detecting HIV, and/**or** HBV, and/**or** HTLV, possibly providing a set of primers to respectively amplify HIV, and/**or** HBV and/**or** HTLV by means of PCR, contacting the biological sample with the probes under conditions which allow hybridization between the probes and target sequences. Maertens specifically indicates that LiPA can be used for determining the type of HBV characterized by incorporating on one and the same strip, probes hybridizing specific to HBV mutants or HBV core, pre-core (see p. 26). Maertens teaches that the probes are immobilized in a line-wise fashion to a membrane strip for reverse hybridization.

27. Maertens does not explicitly teach detecting HBV genotype A specific sequence using a one nucleotide probe.

28. Norder teaches the correlation of HBsAg sequence polymorphisms to HBV genotype A to F based on the comparison of the complete genomic sequences of 27 HBV strains (whole document, particularly Figure 5, p. 499). The genotype A HBV adw2, pBV933, shown in Fig. 5 has nucleic acid sequence 100% identical to the instant SEQ ID NO: 280 (see attached sequence alignment). Norder specifically points out the different amino acids in each genotype, see e.g. Figure 5 and Para bridge 496 and 497; and also in *Discussion*).

29. Okamoto teaches 18 HBV strains, which are classified as genotype A to D, wherein genotype A HBV clone 2, pHBV933, has a nucleic acid sequence 100% identical to the instant genotype A HBV SEQ ID NO: 280, as evidenced by the attached sequence alignment.

30. It would have been obvious to one of ordinary skill in the art to modify Maertens' method to detect the presence of HBV genotype A in a biological sample using a genotype-specific probe designed based on known HBV genotype A sequence taught by Norder and Okamoto. One would have been motivated to do so given the knowledge that line probe assay can be used to

genotype HBV, as taught by Maertens. There would have been a reasonable expectation of success given the knowledge of HBV genomes of different genotypes as taught by Norder and Okamoto. Maertens's method of detecting specific viral nucleic acids using hybridization probes has general applicability. Because a nucleotide is a nucleotide, no matter what virus produced it, it will hybridize to complementary sequence of a probe. Since both Norder and Okamoto provide nucleic acid sequences of HBV genotypes, it is within the ability of one of ordinary skill in the art to select specific probes from known HBV sequences of different genotypes to determine genotype A-specific sequences. Primer/probe design is a routine practice for one of skill in biological laboratories, as illustrated by Maertens. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

31. **(New rejection)** Claims 1 and 28 are rejected under 35 U.S.C. 103(a) as being obvious over Maertens, Okamoto and Norder, as applied to Claims 15, 16 and 29 above, and further in view of McDonough (EP0569237A2, 1993).

32. Claim 15(ii) recites optionally amplifying the HBsAg region, or part thereof, of the HBV gene present in said sample with at least one suitable primer pair; Claim 28 requires that the method of Claim 15, wherein the primer is selected from the group consisting of SEQ ID NOs: 75, 76, 94, 105, 112 and 134-135.

33. The relevance of Maertens, Okamoto and Norder is set forth supra.

34. Neither Maertens, Okamoto nor Norder teaches the primers in Claim 28.

35. McDonough teaches a method of detecting of HBV subtype A, such as HBV*adw*, using amplification oligonucleotides and hybridization probes. McDonough's method comprises the

step of amplifying HBV with oligonucleotide primers, and the step of hybridizing HBV nucleic acids obtained directly or amplified HBV nucleic acids. McDonough indicates that the HBV probes hybridize the genotype A HBV, HBV*adw*, as cited in Ref. Ono *et al* 1983, Nuc. Acids Res. 11(6):1747-1757 (see 2, l.35-l.40). Also as evidenced, Okamoto indicates that that pHBV933 of HBVadw disclosed by Ono is genotype A, see Description of Figure 1, p. 2578. pHBV933 of HBVadw disclosed by Ono has a nucleic acid sequence 100% identical to the instant genotype A HBV SEQ ID NO: 280, see the attached sequence alignment.

36. McDonough teaches use of primers for detecting HBV, wherein SEQ ID NO: 5 is complementary to the instant SEQ ID NO: 75, see alignment below:

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McDonough SEQ ID NO:5     GTTCCATACAACGGGCAAACAGGAG
       SEQ ID NO:75       CAAGGTATGTTGCCCGTTTGTCC
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37. It would have been obvious to one of ordinary skill in the art to amplify the HBsAg region using a suitable primer pair in order to detecting HBV in a sample as taught by Maertens and McDonough. One would have been motivated to do so and have a reasonable expectation of success because McDonouh has shown how to detect HBV by amplifying HBV using suitable primers. Given that HBV sequences are taught by Norder and Okamoto, it is within the ability of one of skill in biology art to make primer/probe based a known HBV sequence as illustrated by McDonough. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Remarks

38. No claim is allowed. HBV genotype A specific target sequences consisting of SEQ ID NO: 77, 140 and 193 are free of the prior art.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph.D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Bo Peng/
Patent Examiner
August 29, 2008